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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,166	08/31/2001	David R. Elmaleh	FLA-003.01	1584

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
05/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/945,166	ELMALEH ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,10 and 25-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/28/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 11, 2007 has been entered.

Claim Rejections - 35 USC § 102 and 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 8, 10, 25-28, 30-32 and 34 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kuijpers et al.

The claims are directed to targeted oligonucleotide constructs comprising a targeting moiety, an antisense oligonucleotide or oligonucleotide analog modified to enhance its efficacy, pharmacokinetic properties or physical properties and an imaging agent suitable for use in PET, SPECT or MRI. In specific embodiments, the imaging agent is a radiolabel, the construct further comprises a therapeutic agent and the antisense oligonucleotide portion of the construct comprises specific modifications.

Kuijpers et al. disclose phosphorothioate antisense oligonucleotides conjugated with a radioisotope. Kuijpers et al. disclose ^{123}I and ^{131}I as specific radioisotopes. These labeled oligonucleotides are disclosed as being useful for targeted therapy of tumors. Kuijpers et al. disclose that the labeled oligonucleotide is targeted to a tumor cell by binding to an antibody oligonucleotide conjugate wherein the labeled oligonucleotide then enters the cell as a therapeutic agent (see scheme 1). The instant specification discloses at page 9 that a targeted construct comprises at least two components that are covalently connected. Thus, Kuijpers et al. disclose a construct containing a targeting moiety that is an antibody, an oligonucleotide and an imaging agent suitable for use in PET, SPECT or MRI. The antisense oligonucleotide of Kuijpers et al. is a therapeutic agent that is derivatized with phosphorothioate, which

increases nuclease resistance and is specific for mRNA, meeting the limitations of claims 25-28, 30-32 and 34.

Although Kuijpers et al. is silent with regard to the ability of the disclosed constructs to cross the blood-brain barrier, because the constructs disclosed by Kuijpers et al. meet the structural limitations of the claims, they are assumed in the absence of evidence to the contrary to have essentially no ability to cross the blood-brain barrier.

Thus, Kuijpers et al. disclose and anticipate claims 1, 5, 8, 10, 25-28, 30-32 and 34.

Claims 1-3 and 5-7 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kayyem et al.

The claims are directed to targeted oligonucleotide constructs comprising a targeting moiety, an antisense oligonucleotide or oligonucleotide analog modified to enhance its efficacy, pharmacokinetic properties or physical properties and an imaging agent suitable for use in PET, SPECT or MRI. Specific embodiments are directed to particular types of imaging agents

Kayyem et al. disclose contrast agent and gene delivery vehicles. The delivery vehicles comprise two polymeric compounds of differing charge with a contrast agent and a targeting moiety attached to one of the polymeric compounds. Kayyem et al. disclose that one of the polymeric compounds can be a nucleic acid so that the delivery vehicle delivers both genetic material and a contrast agent to a cell and is useful for gene therapy. Kayyem et al. disclose at column 4, lines 1-16 that the contrast agent is one suitable for MRI or PET and includes paramagnetic metals such as iron and

gadolinium or radioisotopes such as ^{68}Ga or ^{99}Tc. At column 4, lines 56-62 Kayyem et al. disclose that the targeting moiety includes antibodies, ligands, hormones and peptides. Thus, Kayyem et al. disclose a construct containing a targeting moiety, an oligonucleotide and an imaging agent suitable for use in PET, SPECT or MRI.

Although Kayyem et al. is silent with regard to the ability of the disclosed constructs to cross the blood-brain barrier, because the constructs disclosed by Kayyem et al. meet the structural limitations of the claims, they are assumed in the absence of evidence to the contrary to have essentially no ability to cross the blood-brain barrier.

Thus, Kayyem et al. disclose and anticipate claims 1-3 and 5-7.

Claims 1, 5, 8, 10 and 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuijpers et al. as applied to claims 1, 5, 8, 10, 25-28, 30-32 and 34 above, and further in view of Gewirtz et al. (of record) and Low et al. (of record).

Claims 1, 5, 8, 10, 25-28, 30-32 and 34 are described in the above rejection over Kuijpers et al. Claims 29 and 33 recite that the oligonucleotide portion of the construct is an antisense specific for the C-myb, N-myc, C-myc or PSA genes.

The teachings of Kuijpers et al. are described in the above rejection over this reference. Kuijpers et al. do not teach oligonucleotide constructs containing oligonucleotides that are antisense to C-myb, N-myc, C-myc or PSA genes.

Gewirtz et al. and Low et al. each teach antisense directed to C-myb. Gewirtz et al. teach (see abstract) that oligonucleotides targeted to C-myb are useful in treating hematologic neoplasms. Low et al. teach at column 1, line 15 through column 2, line 25

that C-myb is involved in cellular proliferation and differentiation and that antisense to C-myb is known to inhibit proliferation of several cell lines.

It would have been obvious to one of ordinary skill in the art to use the constructs taught by Kuijpers et al. as useful in targeting oligonucleotides to tumors in order to deliver a C-myb oligonucleotide to a tumor. Because Kuijpers et al. teach a construct for targeting tumor cells and because Low et al. and Gewirtz et al. teach that C-myb is useful in treating cancers, one of ordinary skill in the art would have been motivated to target a C-myb antisense sequence to a tumor using the construct of Kuijpers et al. in order to obtain enhanced delivery of the sequence to tumor cells. One of ordinary skill in the art would have had a reasonable expectation of success in making the construct of Kuijpers et al. with an antisense targeted to C-myb because Kuijpers et al. actually make their construct using techniques well-known in the art and Low et al. and Gewirtz et al. actually make antisense to C-myb using similar synthetic techniques.

Thus, the invention of claims 1, 5, 8, 10 and 25-34 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the rejections over Kuijpers et al. and Kayyem et al. by arguing that both of these references are silent with regard to the ability of the constructs to cross the blood/brain barrier. This is acknowledged but as described in the rejection, because the constructs disclosed in the references meet the structural limitations of the claims they are assumed in the absence of evidence to the contrary to have essentially no ability to cross the blood-brain barrier. Applicants' remarks with

regard to the Moffett and Opalinska references are not addressed because the rejections as amended do not rely on these references.

With regard to the 103 rejection, applicants argue that a *prima facie* case of obviousness has not been provided because Kuijpers et al. is silent with regard to the ability of the disclosed constructs to cross the blood/brain barrier and that Gewirtz et al. and Low et al. do not provide such a teaching. This is not persuasive for the reasons set forth above with regard to the Kuijpers et al. reference.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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